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RESEARCH PAPER

Properties of Fujicalin®, a New Modified Anhydrous Dibasic Calcium Phosphate for Direct Compression: Comparison with Dicalcium Phosphate Dihydrate

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ABSTRACT

The novel, commercially available, free-flowing spherically granulated dicalcium phosphate anhydrous (SGDCPA) Fujicalin for direct tableting was compared with directly compressible dicalcium phosphate dihydrate (DCPD), the properties of which are well known. The two excipients were investigated and compared with regard to their physical and powder properties, compressibility, and compactibility. As a consequence of the spherical shape of its particles, SGDCPA shows the same good flowability and even better compactibility. In contrast to DCPD, SGDCPA shows significant uptake of moisture when exposed to relative humidities (RHs) exceeding 70%. For both excipients, the main deformation mechanism is fragmentation, with SGDCPA yielding significantly stronger tablets.

Key Words: *Dicalcium phosphate dihydrate; Fujicalin; Powder properties; Spherically granulated dicalcium phosphate anhydrous; Tablets*

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INTRODUCTION

Dicalcium phosphate dihydrate (DCPD) is often used in direct compression due to its good flow properties, low hygroscopicity, and low cost (1). However, water of crystallization could possibly be released from this excipient (2,3) (e.g., at elevated temperatures) during processing and thus chemically interact with hydrolyzable drugs (4). This problem can be avoided by using an anhydrous form of calcium phosphate.

A spherically granulated dicalcium phosphate anhydrous (SGDCPA) is commercially available. The two important steps during the manufacturing process of this excipient are restricted crystal growth synthesis (5) to reduce the crystallite size in the product (6) and spherical granulation by spray-drying (7,8).

In the present study, physical properties and bulk powder properties, compressibility, and compactibility of SGDCPA were investigated and compared with those of DCPD.

EXPERIMENTAL

Materials

The SGDCPA, as Fujicalin, was a sample from Fuji Chemical Industry Company, Limited (Yoyama, Japan; batch 98535). The DCPD (DI-CAFOS, batch 7600369; Chemische Fabrik Budenheim, Budenheim, Germany) and magnesium stearate (batch 7645323; Merck KGaA, Darmstadt, Germany) were used as supplied.

Scanning Electron Microscopy

Samples were sputtered with gold/palladium under vacuum. The scans were made using a JSM-6300 scanning electron microscope (SEM) (Japan Electron Optics Laboratory, Ltd., Tokyo, Japan). A Wolfram needle cathode was used in a vacuum of 10^{-3} mm Hg and with a temperature of 2800 K at a distance of 15 mm.

X-ray Powder Diffraction

Measurements were made at room temperature on a Scintag XDS 2000 X-ray powder diffractometer (Scintag Inc., Santa Clara, CA) using monochromatic CuK_α radiation from 2°–35° at a rate of 0.5°/min with a count time of 2.400 s at steps of 0.020.

Differential Scanning Calorimetry

Samples of 2–4 mg of the dried powders in open aluminum pans were studied in a PL differential scanning calorimeter (DSC) (Polymer Laboratories GmbH, Walldorf, Germany) under nitrogen gas purge. The temperature range from 323 K to 573 K was scanned at a rate of 10 K/min Three consecutive samples were tested each.

Thermogravimetric Analysis

Water loss with increasing temperature was recorded for thermogravimetric analysis (TGA) with a Perkin-Elmer TGA 7 (Perkin-Elmer, Ltd., Buckinghamshire, England). The samples had weights between 8 and 20 mg, and the temperature rate was 10 K/min from 303 K to 973 K. Two consecutive samples were tested each.

Moisture Sorption/Desorption Isotherms

Moisture sorption/desorption were measured isothermally with the Dynamic Vapor Sorption DVS 1 (Surface Measurement Systems, Ltd., London, England) at 25°C. The samples were degassed in a vacuum for 2 h at 25°C prior to testing. The gas flow of nitrogen was 200 ml/min; the mass of substance at 0% relative humidity (RH) was 5.1087 mg for DCPD and 4.9621 mg for SGDCPA. One measurement cycle took about 1600 min. The relative humidity range was 0% RH to 95% RH in steps of 10% RH. Stability of a given humidity is ±0.4% RH. The equilibration time after each step was 1 h.

Specific Surface Area

For determining the specific surface area, a Quantachrome NOVA 2200 dual-station, high-speed gas sorption analyzer (Quantachrome GmbH, Odelzhausen, Germany) was used. The samples, which weighed about 3 g, were degassed in vacuum for 18 h and exposed to nitrogen at 77.4 K in a relative pressure range of 1% to 30% (partial pressure of adsorbate/saturation pressure of adsorbate). According to the Brunauer-Emmet-Teller (BET)

equation (9), the specific surface area S_w in m^2g^{-1} was calculated as

$$S_w = 4.37 * V_m \quad (1)$$

with V_m the volume of nitrogen needed to form a monolayer in cm^3g^{-1}. Three consecutive samples were tested each.

Helium Density

The helium density of the particles was determined by gas pycnometry in a Micromeritic Accu Pyc 1330 V2.01 (Micromeritics GmbH, Neuss, Germany). We performed 10 repetitive purge/measure cycles before recording the result. The analysis was performed on four independent samples for each compound; we used a mass of about 45 g for DCPD and about 26 g for SGDCPA. Helium was used as a purge gas.

Loss on Drying

The loss on drying was measured at 105°C for 30 min with a thermo balance (Mettler PM 100 and a Mettler LP 16, Mettler Toledo GmbH, Gießen, Germany). Four consecutive samples with a mass of about 10 g each were tested.

Particle Size Analysis

The particle size distribution of the samples as received was determined using a Helos particle size analyzer (Sympatec GmbH, Clausthal, Germany). In each case, the particle size analysis was performed in quadruplicate with a sample mass of about 1 g in 5% aqueous suspension. On initial measurement, each sample was exposed to the instrument's ultrasound desagglomeration unit for 1 min and measured once more.

To expose the powders to mechanical stress, samples of about 10 g of the powders were shaken on a stainless steel plate using a sieve shaker (Retsch VE 1000, Retsch GmbH and Co. Kg, Haan, Germany) at an amplitude of 1 mm for 90 min. Particle size analysis after the respective treatment was done as described above with four samples each.

Bulk and Tap Densities

Bulk and tap densities were determined according to Pharmacopoeia Europaeia (10) with four repetitions in a 250-ml measuring cylinder (JEL Stampfvolumeter STAV, J. Engelsmann AG, Ludwigshafen/Rhein, Germany). The sample volume of both excipients was about 200 ml, corresponding to 86 g of SGDCPA and 165 g of DCPD. The Hausner coefficient was calculated as the quotient of the tap density and the bulk density.

Flow Test

The 120 cm^3 bulk volume of the excipients was flowed through a brass funnel. The time consumed for flow was measured. The funnel had an inlet diameter of 11 cm and an outlet diameter of 1 cm. The vertical distance between the inlet and the outlet was 21 cm. The tube at the end had a length of about 2 cm. In addition to the flow velocity, the angle of repose was measured using the bottom radius r and the height of the powder heap h.

Tableting Properties

In a 2-L glass bowl, 600 g SGDCPA and 1000 g DCPD were blended with 1% (w/w) magnesium stearate for 10 min at 46 rpm in a Turbula T2C Mixer (Willy A. Bachofen AG/Maschinenfabrik, Basel, Switzerland). The blend was used to compress tablets for determining the tensile strength. In addition, a sieve fraction between 63 μm and 100 μm of DCPD was used and treated in the same way to compare the tensile strength of the tablets with those made of SGDCPA, the mean particle size of which is in this size range.

Deformation measurements were performed with external lubrication to avoid influence of the lubricant on the deformation profiles. Magnesium stearate and propellant F12 were used as an aerosol for external lubrication. Both external lubricated excipient on the one hand and the internal lubricated excipient (blend) on the other hand were compressed in a single-punch instrumented tablet press (Korsch EK0, Korsch GmbH, Berlin, Germany) at 25 rpm. The upper and lower punches were instrumented with a Kistler 9021A piezoelectric pressure transducer (Kistler Instruments GmbH, Ostfildern, Germany) and with two linear variable displacement transducers (Linotast, Novotechnik KG, Ostfildern, Germany). The punches were 9 mm round, flat faced. The data aquisition was managed by noncommercial software (Eccentric Tablet Press Analyzer, Ciba Geigy, K. Jeltsch, 1997). Accuracy of the force

measurement was $\pm 1\%$ of the final value; of the displacement measurement, it was $\pm 10\,\mu m$. Data were analyzed with noncommercial software (BoMa EK0 compression analyzer software, Novartis Pharma AG, Bongartz and Matz, 1999). The Heckel equation was used for obtaining information on the compression properties (11). All tablets were compressed with the same true volume (12), in this case $0.08796\,cm^3$; that is, the tablet masses were 211 mg for DCPD and 250 mg for SGDCPA. The pressure range was adjusted in six steps from 50 ± 10 to 400 ± 10 MPa by adjusting the lower punch.

Tablet Strength

Crushing strength and tablet dimensions were measured with the Tablet Tester Pharma Test WHT-1 (Pharma Test Apparatebau GmbH, Hainburg, Germany). The tensile strength was calculated according to the equation of Fell and Newton (13). We tested 10 tablets per batch.

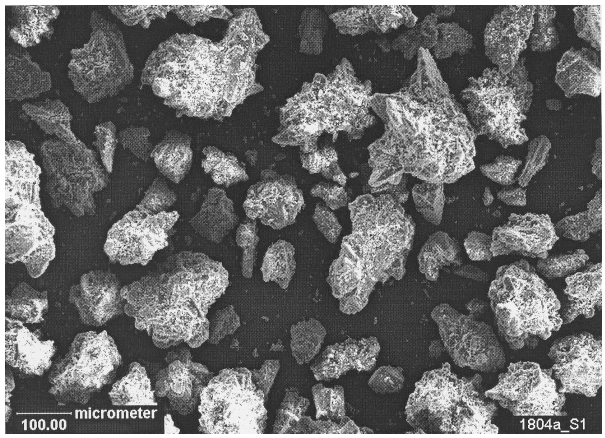
RESULTS AND DISCUSSION

Scanning electron micrographs of DCPD and SGDCPA are shown in Fig. 1a and Fig. 1b at the same magnification. As expected, SGDCPA has a spherical shape caused by its manufacturing process, which includes spray-drying, whereas DCPD also consists of small crystallites, but the granules are irregularly shaped.

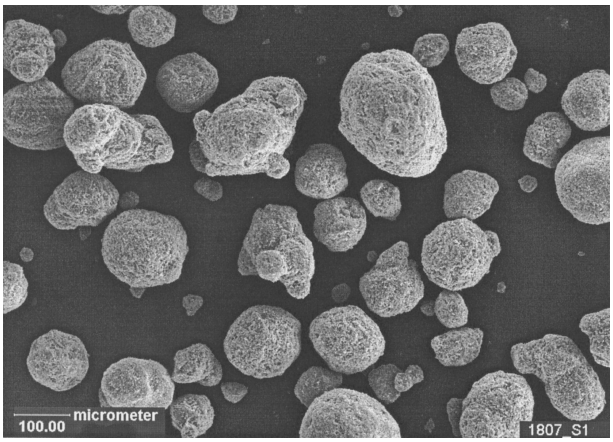
Bulk powder properties of both excipients are summarized in Table 1.

The mean particle sizes of the spherical material (SGDCPA), analyzed with a laser scattering technique, were roughly half of the size of the irregularly shaped (DCPD) particles (Table 1). The particle size distribution shows the same spread in both cases, that is, about 120 μm for $Q16\%$–$Q84\%$. Using ultrasound to study mechanical resistance of the particles, mean particle size of SGDCPA was reduced by a factor of roughly 10 (Table 1), whereas the mean particle size of DCPD stayed widely unaffected.

Although the mean particle size of SGDCPA was nearly half the size of DCPD, the flowability and the angle of repose were nearly equal for both excipients (Table 1). It is presumed that the small particle size and about 100 times larger specific surface area of SGDCPA (Table 1) has a negative effect on the flowability of SGDCPA, which is compensated by the spherical shape of SGDCPA granules.



(a)



(b)

Figure 1. Scanning electron micrographs: (a) DCPD; (b) SGDCPA.

The Hausner coefficients of the two substances were not significantly different from each other (Table 1). This is in accordance with the finding of equal flowability.

X-ray powder diffraction scans of DCPD and SGDCPA are given in Fig. 2. DCPD had the crystal structure of brushite, JCPDS pattern 09-0077 (14), was monoclinic and of high crystallinity. SGDCPA had triclinic crystals and the structure of monetite, JCPDS pattern 70-1425 (14).

The absence of water of crystallization in the crystal structure of SGDCPA caused a more com-

Table 1

Different Properties of Spherically Granulated Dicalcium Phosphate Anhydrous (SGDCPA) and Dicalcium Phosphate Dihydrate (DCPD)

	SGDCPA	DCPD
Mean particle size (μm)	94.2 ± 0.9	176.8 ± 1.6
Q16% (μm)	18.44	119.83
Q84% (μm)	149.20	237.07
Mean particle size after vibration (μm)	90.3 ± 0.8	169 ± 1.5
Mean particle size after ultrasound (μm)	7.7 ± 0.06	163.1 ± 1.5
Flow of 120 cm^3 bulk volume (s)	10.1 ± 0.2	10.4 ± 0.3
Angle of respose (°)	24.5 ± 1.1	27.5 ± 1.5
Bulk density (g/cm^3)	0.431 ± 0.042	0.827 ± 0.053
Tap density (g/cm^3)	0.484 ± 0.029	0.930 ± 0.030
Hausner coefficient	1.123 ± 0.128	1.125 ± 0.076
Specific surface area (m^2/g)	27.01 ± 0.03	0.30 ± 0.03
Bulk porosity (%)	84.8	65.3
Tap porosity (%)	82.9	61.0
Helium density (g/cm^3)	2.841 ± 0.033	2.385 ± 0.027
Loss on drying (%)	0.5 ± 0.1	2.8 ± 0.3

Each number represents the mean value ± standard deviation ($n = 4$).

pact packing with a reduced unit cell volume (15,16). This reduced unit cell volume is reflected by a higher helium density compared to that found for DCPD (Table 1).

The sorption/desorption isotherm of DCPD in Fig. 3a shows that only a minor amount of water was adsorbed in the humidity range 20%–70% RH. In contrast to DCPD, SGDCPA took up 20 to 50 times more water (Fig. 3b; note the altered scaling). At 90% RH, DCPD contained only a total of about 0.1% adsorbed moisture, whereas SGDCPA contained 4.0% water. Apart from other crystal surface properties, presumably the much higher specific surface area of SGDCPA contributes to its increased water uptake, a behavior that was found for other types of calcium phosphate materials (e.g., DI-CAFOS AN, DI-CAFOS A) as well (17).

The TGA profiles of both SGDCPA and DCPD (Fig. 4) show a small weight loss below 105°C, which presumably is caused by the removal of adsorbed water from the particle surfaces. In the case of SGDCPA, the loss of water was below 0.5%. Water of crystallization in DCPD, which was more strongly bound within the crystal lattice, was only lost at temperatures well above 100°C. The total weight loss (%) up to a temperature of 300°C was 21.1%, which corresponds to the theoretical water content per unit mass in DCPD, which is 20.9%.

Furthermore, the TGA profile of DCPD (Fig. 4) indicates that this excipient loses water in two steps at about 150°C and 190°C (18,19). The rate and amount of dehydration is influenced not only by the temperature and humidity in the surrounding atmosphere (20), but also by particle size (21) and specific surface area.

In the case of DCPD, the water loss in TGA corresponds roughly to the respective DSC trace (Fig. 5). The first endothermic signal at about 140°C is attributed to the loss of half a mole of water from DCPD (22):

$$Ca_2(HPO_4)_2{*}\,4H_2O \rightarrow Ca_2(HPO_4){*}\,3H_2O + H_2O$$

The distinct peak at about 185°C coincides well with further loss of 3 moles of water, initializing the formation of anhydrous calcium hydrogen phosphate:

$$Ca_2(HPO_4)_2{*}\,3H_2O \rightarrow Ca_2(HPO_4)_2 + 3H_2O$$

There is a transition of the anhydrous salt into calcium pyrophosphate at a temperature of about 430°C:

$$Ca_2(HPO_4)_2 \rightarrow Ca_2P_2O_7 + H_2O$$

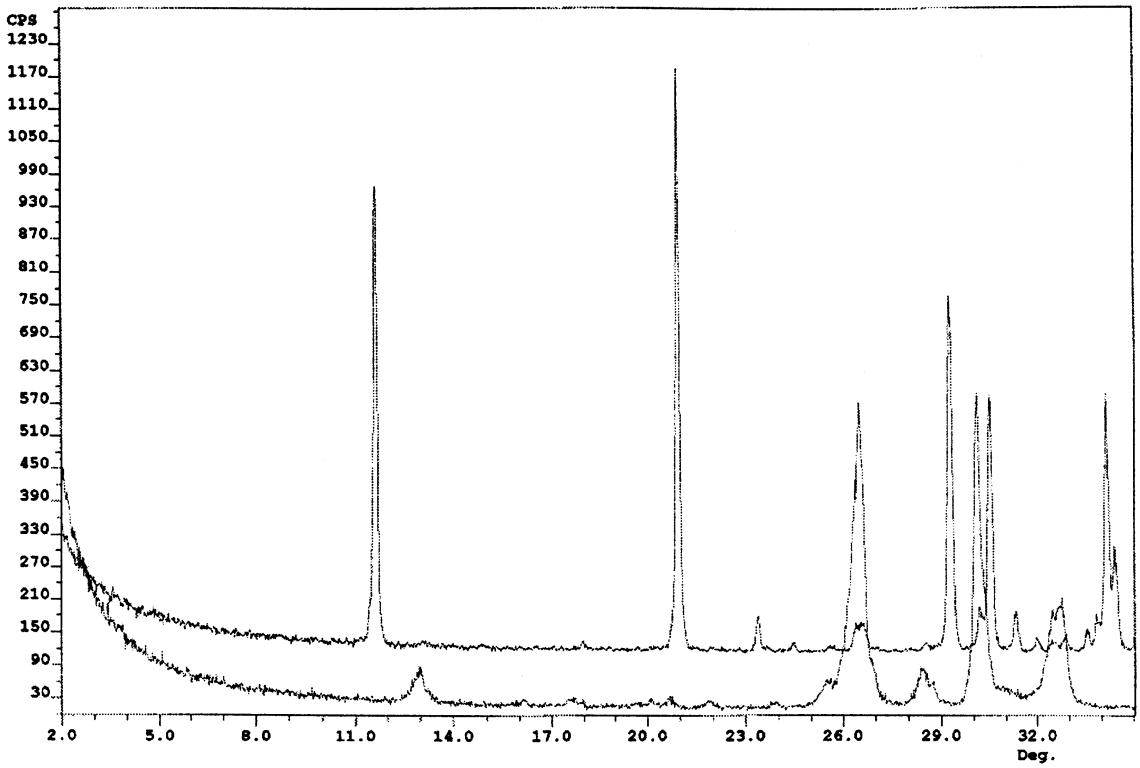


Figure 2. X-ray diffraction scans of DCPD (upper curve) and SGDCPA (lower curve).

In the case of SGDCPA, only the transition to calcium pyrophosphate can be seen in the TGA plot (Fig. 4). The DSC trace for this excipient, therefore, shows nearly no change in the heat flow over the measured temperature range up to 300°C and is therefore not shown.

From both materials, tablets were compressed at six distinctive maximum pressures in the range 50–400 MPa with external lubrication. Fig. 6 shows the minimum porosities of the respective compacts at maximum compression pressure. As found for the bulk and tap porosities of the powder materials, porosity of the compacts of SGDCPA was significantly higher over the whole range of compression pressures. The difference in porosities and the change of porosity of SGDCPA and DCPD are nearly constant over the whole pressure range. The two excipients have a relation of porosities under pressure that corresponds to the relation of their bulk and tap densities (Table 1). Particularly for SGDCPA, there is a relatively large amount of void that, even under high pressure, can hardly be reduced.

The behavior of a substance to resist an external force/pressure is expressed as the *yield pressure*, which is defined as the reciprocal of the slope values obtained from the Heckel plots (Fig. 7a; 23), where the logarithm of the reciprocal of porosity is plotted versus the maximum compaction pressure. The values of the yield pressures found for both of the substances are of the same magnitude and are high (e.g., a yield pressure of about 300 MPa for an applied pressure of about 150 MPa) (Fig. 7b), which usually is attributed to fragmentation as the main consolidation mechanism (24,25). The yield pressure values for SGDCPA are higher than the values for DCPD (Fig. 7b), which means a higher resistance toward the deformation of the powder bed. This is in contrast to the fact that its particles were less resistant to fragmentation caused by ultrasound, as described above.

Elastic "in die" recovery was measured as the difference of the height of the compact at maximum force and when contact to the upper punch was lost. The elastic recovery was significantly higher

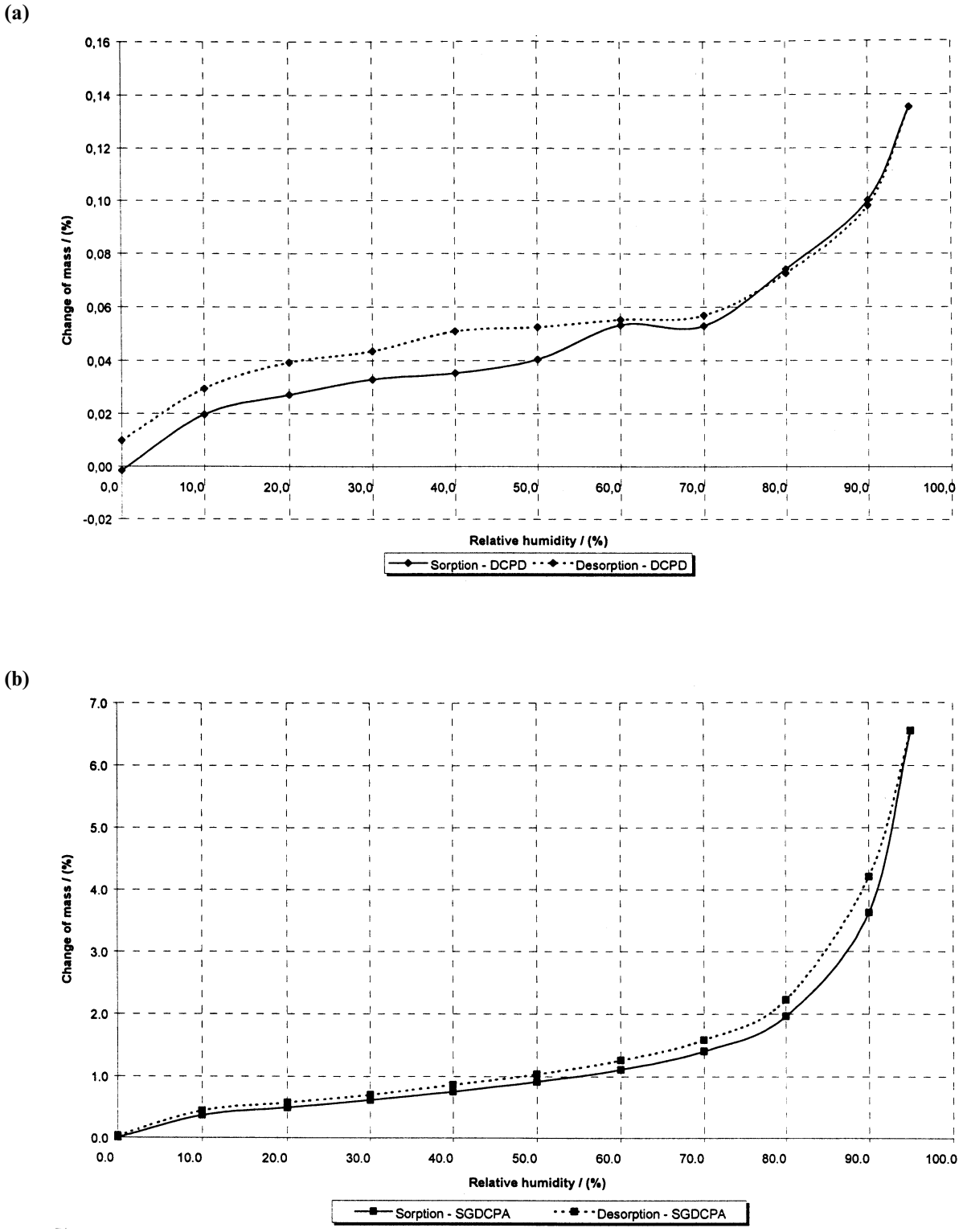


Figure 3. (a) Sorption/desorption isotherm with the change of mass of DCPD plotted against the relative humidity; (b) sorption/desorption isotherm of SGDCPA with change of mass of SGDCPA plotted against the relative humidity.

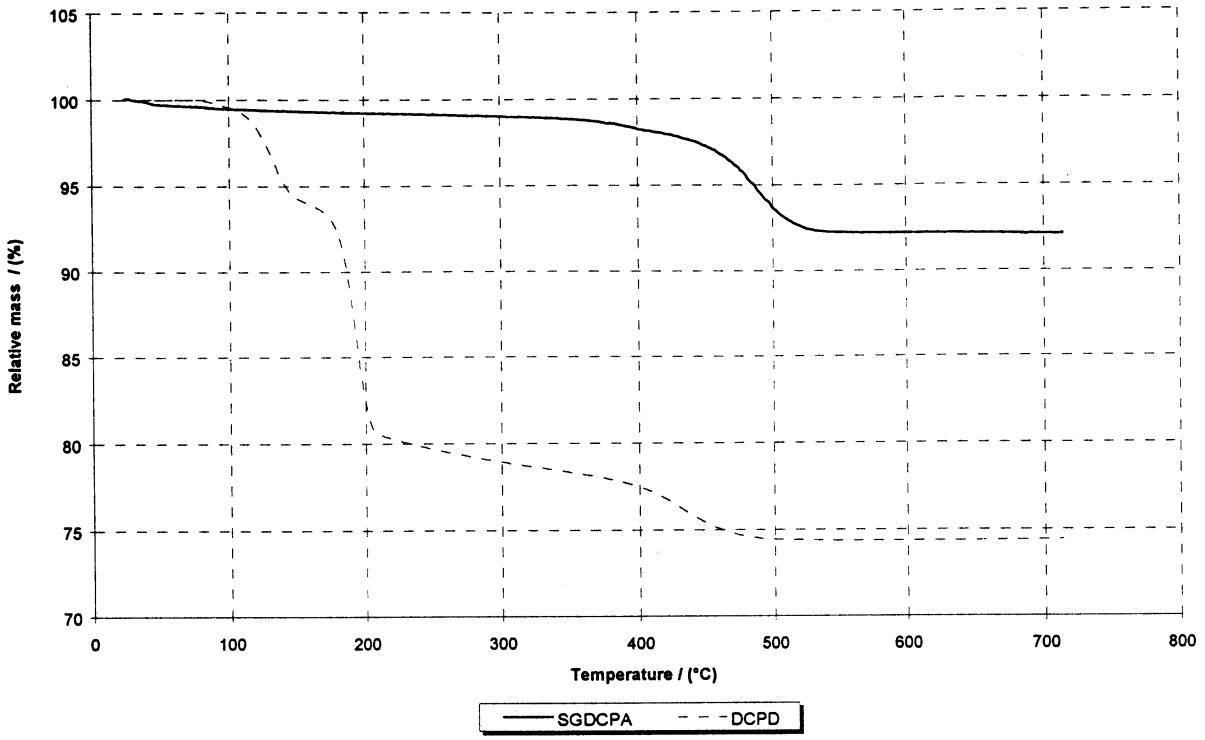


Figure 4. TGA profiles of SGDCPA and DCPD with relative mass plotted against the temperature.

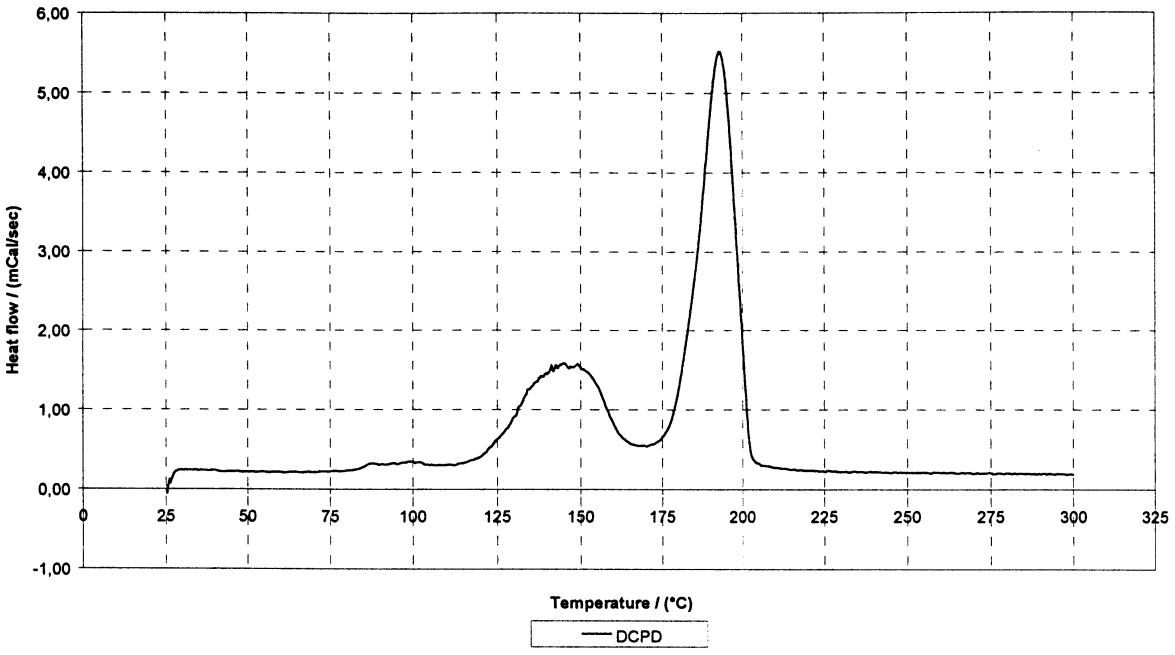


Figure 5. DSC profile of DCPD with heat flow plotted against the temperature.

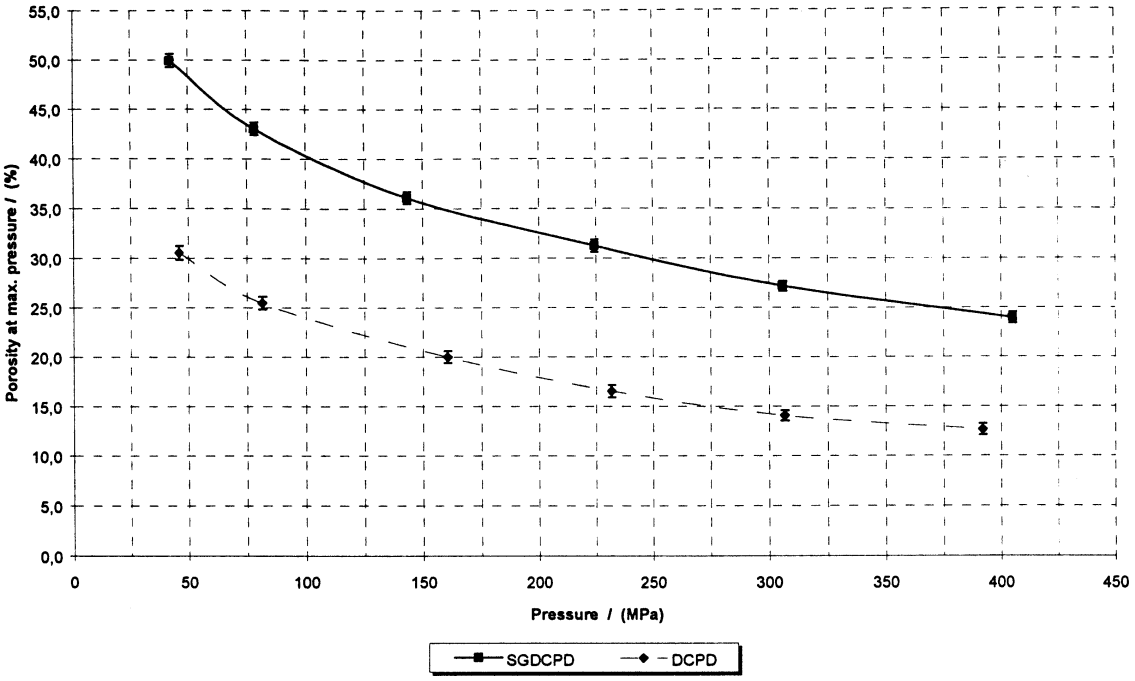


Figure 6. The porosity at maximum pressure of SGDCPA and DCPD plotted against the applied pressure. Each point represents the average plus or minus the standard deviation of four trials.

for SGDCPA than for DCPD over the whole range of compaction pressures studied (Fig. 8).

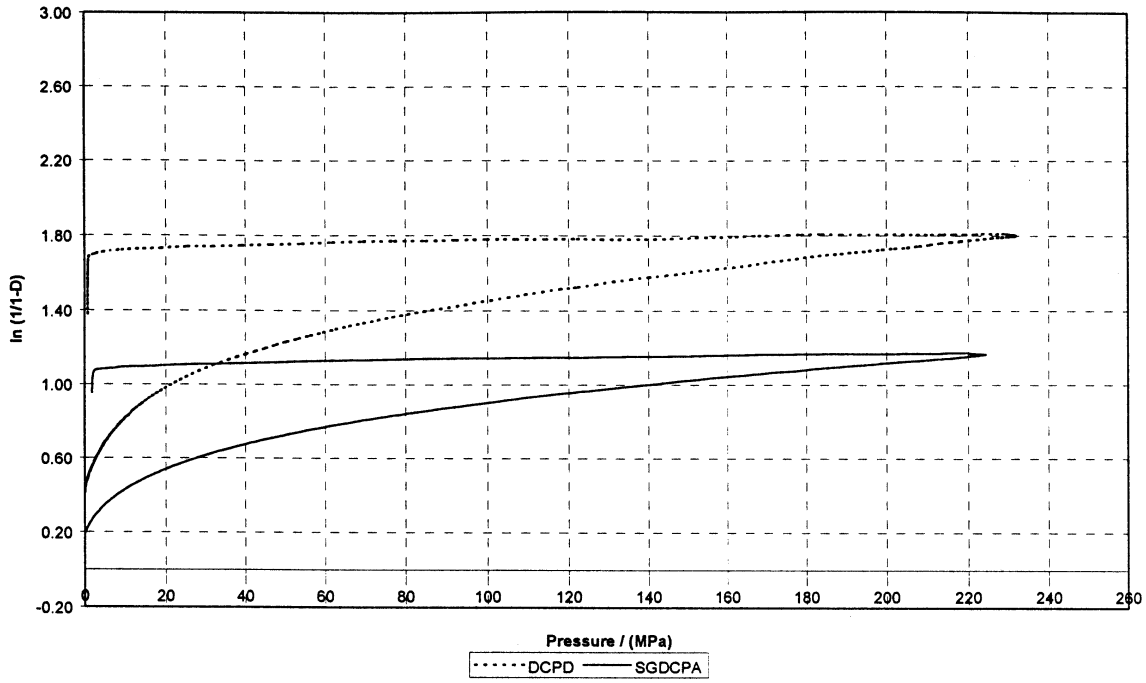
Higher elastic recovery inside the die in this case, however, does not lead to weaker tablets or reduced compactibility (Fig. 9). The tensile strength of SGDCPA tablets was higher by a factor of more than 4 compared to DCPD. It is known that particle size affects compact strength. In the case of DCPD, tensile strength of the compacts was higher with a smaller particle size (26; Fig. 9). Even if fractions with nearly the same mean particle sizes of the two excipients are directly compared with each other, SGDCPA compacts to tablets of about three times higher tensile strength compared with DCPD. As typical for brittle materials, SGDCPA shows almost no reduction in tablet strength at all when more lubricant is added; in the present study, 2% magnesium stearate was used (25).

CONCLUSIONS

Fujicalin, a spherically granulated anhydrous dicalcium phosphate (SGDCPA), has a lower mean particle size and, because of the high porosity of the particles, an extremely high specific surface area in comparison to directly compressible dicalcium phosphate dihydrate (DCPD). As a result of the spherical shape of SGDCPA, its flowability is as good as that of DCPD. Mechanical stress by extended vibration does not reduce the particle size of SGDCPA. Therefore, a decrease in the particle size during regular processing is not expected. Compared with DCPD, SGDCPA takes up significantly more moisture from its environment, but a rather small total amount of water loss was measured during the thermogravimetric analysis up to 105°C, for which less than 0.5% was released. If the excipient is stored and processed under low relative humidity (< 70% RH), extended interactions of adsorbed water and a hydrolyzable drug are widely not to be expected.

The total moisture contents of both excipients studied were relatively low. Their difference presumably had no significant influence on the tensile strength of the tablets. Adsorbed water vapor neither increases nor decreases the tablet strength for a substance of low solubility, as was found for dicalcium phosphate dihydrate and acetylsalicylic acid (27). A high tensile strength for SGDCPA

(a)



(b)

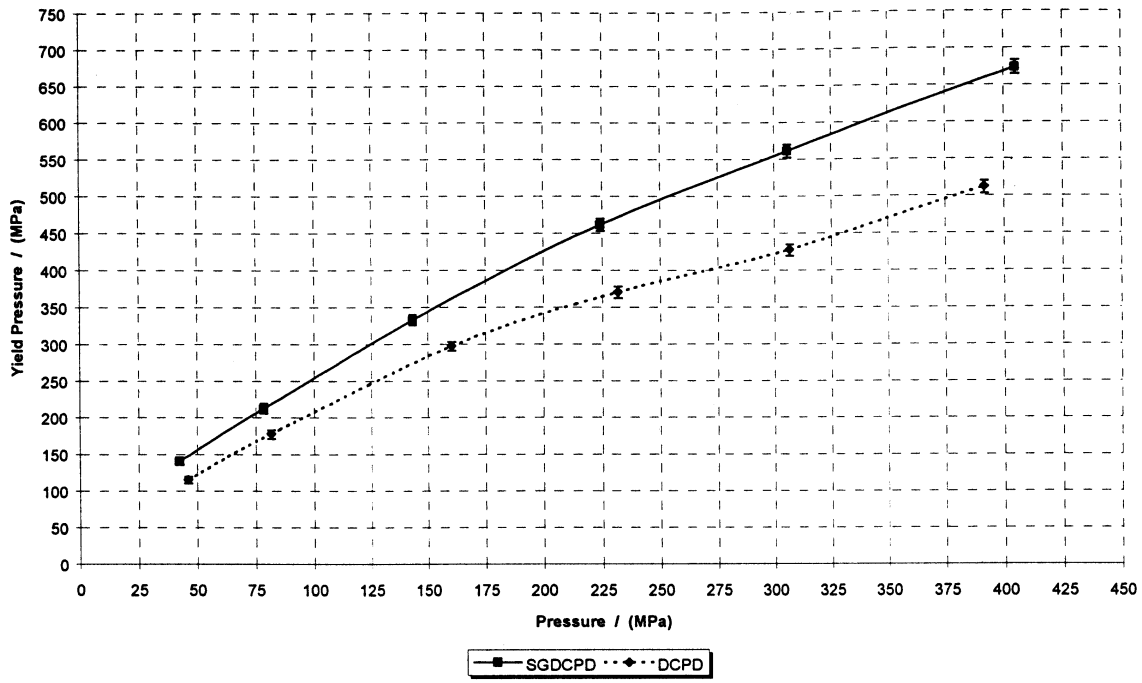


Figure 7. (a) Heckel plots of DCPD and SGDCPA with the Heckel values (ln(1/porosity)) plotted against the applied pressure; (b) the yield pressure of SGDCPA and DCPD plotted against the applied pressure, with each point representing the average plus or minus the standard deviation of four points.

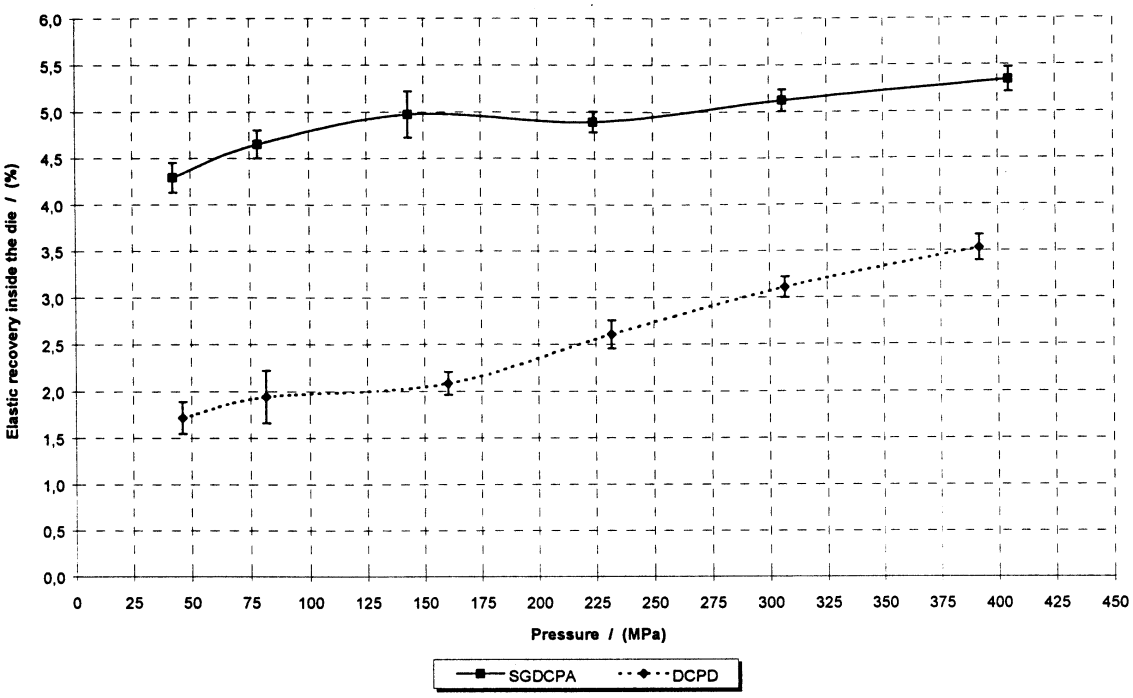


Figure 8. The elastic recovery inside the die of SGDCPA and DCPD plotted against the applied pressure. Each point represents the average plus or minus the standard deviation of four trials.

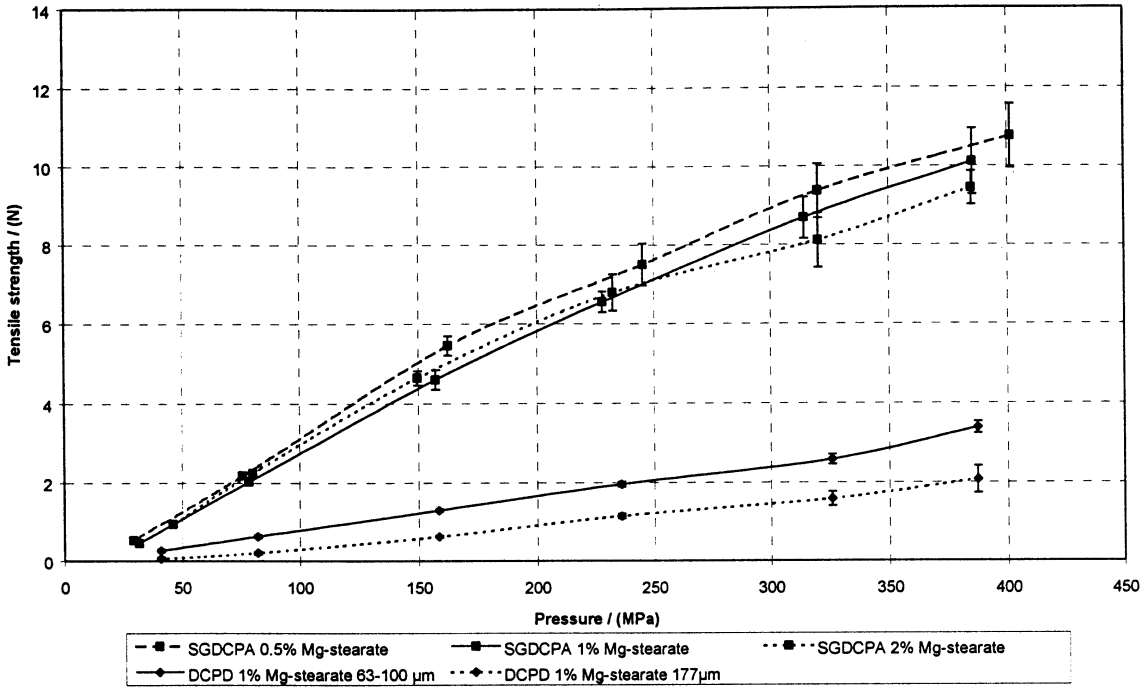


Figure 9. The tensile strength of SGDCPA and DCPD plotted against the applied pressure. For SGDCPA, the amount of lubricant was in the range 0.5% to 2.0%. DCPD had different mean particle sizes.

tablets was found, a fact that only to a minor degree is attributed to its small mean particle size. The main effect should presumably be the extremely high specific surface area of the particles contributing to a huge number of contact sites and strong cohesion of SGDCPA (28). As a consequence of the above-mentioned powder properties, the tensile strength of the SGDCPA compacts was much higher, although DCPD showed less elastic recovery. Like other brittle materials, SGDCPA showed nearly no reduction in tablet strength with increasing lubricant fraction.

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